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Original article

Surgical management of hyperthyroidism

C. Quérat[a,*], N. Germain[b], J.-M. Dumollard[c], B. Estour[b], M. Peoc'h[c], J.-M. Prades[a]

[a] Service ORL et de Chirurgie Cervico-Faciale, Hôpital Nord, CHU de Saint-Étienne, 42055 Saint-Étienne cedex 2, France
[b] Service Endocrinologie – Diabète et Maladies Métaboliques, Hôpital Nord, CHU de Saint-Étienne, 42055 Saint-Étienne cedex 2, France
[c] Laboratoire d'Anatomie et Cytologie Pathologique, Hôpital Nord, CHU de Saint-Étienne, 42055 Saint-Étienne cedex 2, France

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ABSTRACT

Aims: Hyperthyroidism includes several clinical and histopathological situations. Surgery is commonly indicated after failure of medical treatment. The aim of this study was to analyze the indications and complications of surgery as well as endocrine results.
Materials and methods: Patients operated on for hyperthyroidism between 2004 and 2012 were included in a retrospective study. Total thyroidectomy was performed for Graves' disease, toxic multinodular goiter and amiodarone-associated thyrotoxicosis; patients with toxic nodule underwent hemithyroidectomy. Pathologic analysis assessed surgical specimens; postoperative complications and resolution of hyperthyroidism were noted.
Results: Two hundred patients from 15 to 83 years old were included. One hundred and eighty-eight underwent primary surgery and 12 were re-operated for recurrent goiter (6 with subtotal thyroidectomy for multinodular goiter 25 years previously; 6 with hemithyroidectomy for solitary nodule 15 years previously). Eighty-two patients suffered from toxic multinodular goiter, 78 from Graves' disease, 35 from solitary toxic nodules and 5 from amiodarone-associated thyrotoxicosis. Fourteen papillary carcinomas (including 11 papillary microcarcinomas) and 34 healthy parathyroid glands (17%) were identified in the pathological specimens. Postoperative complications comprised 4% permanent recurrent laryngeal nerve palsy (1 year follow-up), 9% hematoma requiring surgical revision, and 3% definitive hypocalcemia. Normalization of thyroid hormone levels was observed in 198 patients. Two recurrences occurred due to incomplete resection (1 case of Graves' disease and 1 intrathoracic toxic goiter that occurred respectively 18 and 5 months after resection). Postoperative complications were more frequent in multinodular goiter (23%) than in Graves' disease (13%) (ns: $P > 0.05$).
Conclusion: Surgical management of hyperthyroidism enables good endocrinal control if surgery is complete. Patients need to be fully informed of all possible postoperative complications that could occur, especially vocal ones. Long-term follow-up is necessary to detect recurrence, which can occur more than 20 years after partial thyroidectomy surgery. Surgery allows early diagnosis of 12.5% of papillary carcinomas.

1. Introduction

Hyperthyroidism is defined as excessive secretion of iodinated thyroid hormones: triiodothyronine (T3) and thyroxine (T4). The associated target tissue disorders are known as thyrotoxicosis. Asthenia, weight-loss, anxiety, palpitations and thermophobia are the main symptoms [1]; associated with goiter or exophthalmia, they are suggestive of this metabolic disorder.

Hyperthyroidism affects 1–3% of the general population: 2% of female and 0.2% of male subjects [1]. Anatomo-clinical situations vary: the most frequent is Graves' disease, accounting for 50–80% of cases [2].

Other causes comprise toxic multinodular goiter (MNG), toxic adenoma and amiodarone-associated hyperthyroidism.

Several treatment options are available, depending on the pathology involved: synthetic anti-thyroid drugs (SATDs), radioactive iodine, percutaneous ethanol injection, or surgery.

Treatment choice has long been controversial. The risk of postoperative complications such as hypocalcemia [3], hematoma or recurrent laryngeal nerve palsy (RLNP) [4] following total

Abbreviations: SATDs, synthetic anti-thyroid drugs; MNG, multinodular goiter; RLNP, recurrent laryngeal nerve palsy; STT, subtotal thyroidectomy; TT, total thyroidectomy.

* Corresponding author.
E-mail address: c.querat@yahoo.fr (C. Quérat).

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Table 1
Preoperative demographic data.

	n (%)	Gender F/M	Age (years)	Primary surgery		Secondary surgery	
				n	Age	*n*	Age
MNG	82 (41%)	33/8	55.7	65 (79%)	55	17 (21%)	61
Graves' disease	78 (39%)	34/5	38.7	40 (51%)	41	38 (49%)	36.5
Solitary nodule	35 (17.5%)	26/9	48.8	29 (83%)	48	6 (17%)	53.8
Amiodarone	5 (2.5%)	1/4	63.2	5 (100%)	63.2	0	
Total	200	4/1	51.6	139 (69.5%)	51.8	61 (30.5%)	50.4

MNG: multinodular goiter; *n*: number of cases.

thyroidectomy (TT) is classically elevated in case of hyperthyroidism, but surgery provides faster and more stable remission of endocrine disorder than conservative strategies [1], and also earlier detection of thyroid cancer associated with endocrinopathy [5]. Surgery is therefore a treatment of choice, notably following failure of primary medical treatment (usually SATDs and/or radioactive iodine) [1].

The present study sought to analyze indications for and complications associated with surgery, and endocrine results according to pathology.

2. Materials and methods

A retrospective study included patients operated on for hyperthyroidism by a single surgeon between 2004 and 2012. TT was performed for Graves' disease, toxic goiter and amiodarone-associated hyperthyroidism, and lobo-isthmectomy for toxic nodule.

Two hundred patients (38 male [19%], 162 female [81%]), mean age 48 years (range, 15–83 years), were included over the 8-year period. In 139 cases (69.5%), surgery was primary, and in 61 (30.5%) secondary to either medical treatment or prior surgery.

Table 1 presents the main demographic data.

SATDs were prescribed in first intention except for patients poorly tolerating this medication or requiring urgent surgery, in which case beta-blockers were used.

Surgery was in all cases performed under general anesthesia with intubation. Inferior laryngeal nerve monitoring was not systematically used. Redon drains were systematically fitted until postoperative D2.

Hospital stay was systematically for 48 hours. Preoperative and postoperative nasofibroscopy (D2 and 1 month) were performed in all cases. In patients with postoperative laryngeal immobility, a minimum one-year of follow-up was achieved.

Calcemia was systematically assessed by D1, D2, D7 and D14, and at 2 months if not normal by D14.

All thyroidectomy specimens underwent pathologic analysis searching for resected parathyroid gland and thyroid carcinoma.

Transient and definitive hypocalcemia, RLNP (definitive if persistent at 12 months), hematoma requiring surgical revision and recurrent endocrinopathy were recorded.

Statistical analysis used Chi^2 or Fisher exact test; the significant threshold was set at 0.05.

3. Results

Surgical strategy was determined by various factors: desire for pregnancy, carbimazole-induced agranulocytosis, compressive signs, suspect cytology, and ophthalmopathy.

Twelve of the 61 patients for whom surgery was deferred (6%) had had previous procedures: 6 subtotal thyroidectomies (STT) for goiter 25 years before index surgery, and 5 lobo-isthmectomies for solitary nodule 15 years or, in 1 case, 30 years before index surgery. Forty-nine (24.5%) were operated on following medical failure (23 with recurrence at a mean 5 years; 18 failures of ongoing medical treatment including 5 cases of carbimazole-induced agranulocytosis). Eight patients had previously received ≥ 1 dose of iodine 131. Fig. 1 presents the factors for treatment strategy.

Pathologic specimen analysis detected 25 malignant lesions (12.5%): 3 papillary thyroid carcinomas (1.5%) and 22 papillary microcarcinomas (11%). A healthy parathyroid gland was resected in 17% of cases (34 patients). Table 2 shows pathology results.

Table 3 presents the main complications.

There were no deaths during follow-up.

Of the 18 patients (9%) with postoperative hematoma, 17% were on anticoagulation treatment compared to 13% of patients without (ns: $P = 0.6$).

RLNP was noted in 4 patients preoperatively and a further 13 postoperatively, 5 of whom recovered normal laryngeal motion within the year. Two patients had laryngeal diplegia: unilateral laser cordectomy was performed on the day of primary surgery in 1 case and 1 month later in the other; no tracheotomy was required. Six months after surgery, clinical evaluation noted intelligible voice, with 1 mobile vocal fold and the other immobile in a paramedian position. In the other patient bilateral palsy and dysphonia was noted at 1 year. There was no RLNP in patients undergoing revision surgery for compressive hematoma.

Twenty percent of patients had hypocalcemia by D2, definitive in only 3%; 9% of patients with resected parathyroid gland developed definitive hypocalcemia; preserved parathyroid gland was associated with 2% definitive hypocalcemia; the difference, however, was non-significant ($P > 0.05$).

After surgery, 2 cases of recurrence were noted (1% of patients): 1 of Graves' disease after STT, and 1 intrathoracic nodule left after MNG resection 5 months previously.

4. Discussion

4.1. Treatment indications

In thyrotoxicosis, hyperthyroidism requires rapid treatment to avoid recurrence and allow amiodarone treatment if necessary. Strategy depends on pathology, health status and acceptable risk [1].

In Europe, SATDs are the first-line attitude in Graves' disease. They are usually effective, but only within 4–6 weeks, and require prolonged treatment, cross-placental and lacteal barriers and may exceptionally (< 1%) induce agranulocytosis [1]. Above all, long-term efficacy is only moderate, with a 50% relapse rate at 1 year [6].

Radioactive iodine may be a first-line attitude in Graves' disease and small MNG [1], and is the second-line treatment of choice after failure of SATDs in Graves' disease. However, it is limited by numerous contraindications, and the rate of failure is estimated at 21% [7].

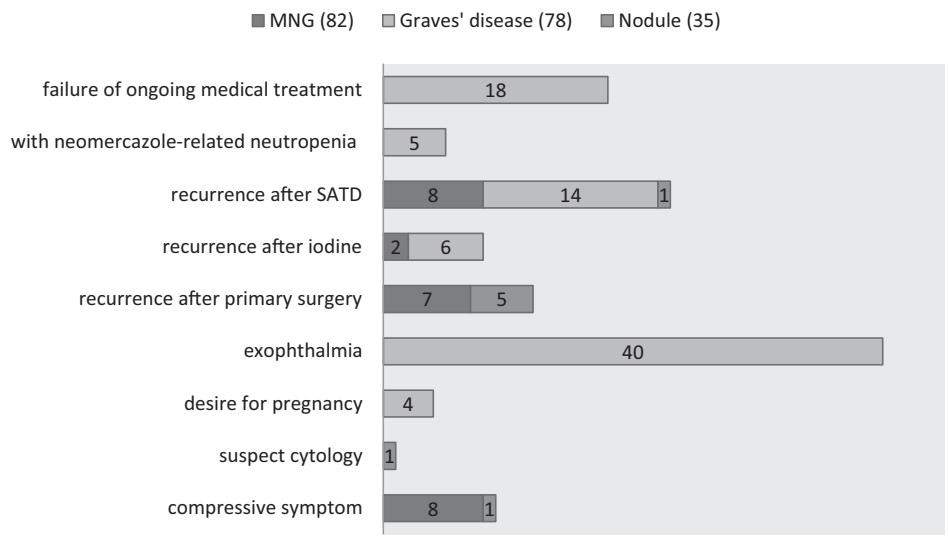

Fig. 1. Factors guiding therapeutic decision-making. MNG: multinodular goiter; ttt: treatment; SATDs: synthetic anti-thyroid drugs.

Table 2
Pathology results on specimen.

	Papillary carcinoma	pμc	Malignant lesion	Benign lesion	Parathyroid+
MNG (82)	3 (3.6%)	11 (13.4%)	14 (17%)	68 (83%)	12 (15%)
Graves' disease (78)	0	8 (10.2%)	8 (10.2%)	70 (90%)	10 (13%)
Nodule (35)	0	3 (8.6%)	3 (8.6%)	32 (91.5%)	12 (34%)
Amiodarone (5)	0	0	0	5 (100%)	0 (0%)
Total (200)	3 (1.5%)	22 (11%)	25 (12.5%)	175 (87.5%)	34 (17%)

MNG: multinodular goiter; pμc: papillary microcarcinoma; parathyroid+: intra-specimen parathyroid gland.

Table 3
Postoperative complications.

	RLNP at 2 months	Definitive RLNP	Transient hypoCa	Definitive hypoCa	Hematoma	Total definitive complications
MNG (82)	8 (10%)	6 (7.3%)	19 (23.1%)	4 (4.8%)	9 (11%)	10 (12%)
Graves' disease (78)	3 (3.8%)	1 (1.3%)	16 (20.5%)	2 (2.5%)	7 (9%)	3 (4%)
Nodule (35)	1 (2.8%)	0	4 (11.4%)	0	2 (5.7%)	0
Amiodarone (5)	1 (20%)	1 (20%)	1 (20%)	0	0 (0%)	1 (20%)
Total (200)	13 (6.5%)	8 (4%)	40 (20%)	6 (3%)	18 (9%)	14 (7%)

RLNP: recurrent laryngeal nerve palsy; hypoCa: hypocalcemia; MNG: multinodular goiter.

In solitary nodule, percutaneous ethanol injection has been described when surgery is not feasible; the rate of failure is around 14%.

The main factors guiding treatment are goiter size and compressive signs on imaging (AP chest X-ray or CT), suspected or diagnosed concomitant thyroid carcinoma, desire for pregnancy, and ophthalmopathy [1]. In et al. [8] claim TT to be the most effective option in recurrent Graves' disease, from both a medical and an economic point of view.

4.2. Surgical techniques

In Europe until the 2000s, STT was preferred, to avoid permanent postoperative opotherapy [9]. TT is now indicated, both in Graves' disease and MNG, providing optimal endocrine control without significantly elevated risk of hypocalcemia or RLNP [10].

In recent years, inferior laryngeal nerve monitoring was developed for intra-operative laryngeal nerve assessment [9]; some studies reported reduced transient RLNP, but most did not note a significant benefit [12,13].

4.3. Postoperative complications

Surgery, unlike medical management, allows screening and early treatment of thyroid carcinoma. The rate of thyroid cancer in hyperthyroidism is non-negligible: 12.5% thyroid carcinoma rate in the present study, and up to 18.3% in thyroidectomy specimens reported elsewhere [5].

There were 34 parathyroid glands resected within the 200 specimens (17%), with 20% transient and 3% definitive hypocalcemia. Parathyroid resection can induce transient hypocalcemia, but in the current series did not correlate with postoperative hypocalcemia. Nair et al. [14] found hypocalcemia following TT to be significantly associated with parathyroid resection ($P = 0.006$). Overall definitive hypocalcemia rates range from 0.4% to 4.2% [3,10], independently of whether TT or STT was performed [15].

The present study noted a 6.5% rate of transient RLNP, 4% definitive RLNP and 1% laryngeal diplegia, in agreement with the literature. Relative risk for RLNP was 1.54 in Guo et al.'s meta-analysis [15]; rates vary from 1% [16] to 13% [17]. These studies, however, did not always allow for the fact that the patients were in a situation of hyperthyroidism or had had prior surgery. Hyperthyroidism is associated with a 2.5-fold higher risk of RLNP than in thyroid

surgery under euthyroidism [18]. Likewise, in revision surgery, RLNP risk may reach 17%. Laryngeal diplegia rates vary, depending on the series, from 0.4% to 1.7% [19,20], requiring tracheotomy in 0.3% of cases [19]. In the present study with hyperthyroidism in all cases, 25% of patients who developed definitive RLNP had undergone prior surgery. No tracheotomies were required.

Nine percent of patients developed postoperative hematoma; anticoagulation treatment did not significantly increase this risk ($P > 0.05$). However, low molecular weight heparin relay was systematic and withdrawn 12 hours before surgery. Lang et al. [21] reported a 0.7% postoperative hematoma rate, but Godballe et al. noted a 4.2% incidence for this complication [22]. In these reports, male gender and extensive resection were considered to be risk factors. Lang et al. [21] also noted that previous thyroid surgery increased risk 4-fold. Hyperthyroidism may increase the risk for postoperative hematoma: Chiang et al. [23] noted a 11.5% rate for hematoma after thyroidectomy for Graves' disease, and a 6.5% incidence for this complication in euthyroidism patients.

In the present study, whatever the procedure (lobo-isthmectomy, TT or totalization) used, postoperative complication rates did not differ (definitive RLNP, $P = 0.9$; definitive hypocalcemia, $P = 0.36$; hematoma, $P = 0.5$). Hyperthyroidism thus indeed seemed to be the determining factor in Graves' disease and toxic MNG.

4.4. Endocrine results

Two patients had recurrence of primary pathology. In 1, operated on for MNG, an intrathoracic nodule had been left after the initial surgical procedure 5 months earlier. In the other, there was recurrence of Graves' disease 18 months after STT. According to the literature, surgery using TT is the most effective treatment modality in the long-term: Genovese et al. [7] reported a 0.3% recurrence rate of hyperthyroidism after TT, compared to a 10% incidence with STT. Bilosi et al. [24] demonstrated that the recurrence rate could be as high as 14% if more than 6 g of parenchyma was left after surgery. In these various reports as in the present study, follow-up did not exceed 5 years; but in our series 6% of patients had undergone previous surgery. In unilateral thyroidectomy, recurrence was of rapid onset: 5 lobo-isthmectomy patients recurred at 15 years, compared to 25 years in the 6 cases of STT. TT is to be preferred, to avoid recurrence of hyperthyroidism. Even infraclinical hyperthyroidism increases cardiovascular risk: hypertension, ischaemic heart disease and atrial fibrillation [25].

5. Conclusions

Surgery is the treatment of choice for rapid definitive control of hyperthyroidism, especially in Graves' disease, MNG and amiodarone-associated hyperthyroidism. Surgery must, however, be complete; otherwise, residual thyroid tissue will lead to even very late recurrence (later than 20 years). Complications may be definitive, and require full patient information. Only surgery allows early diagnosis of associated papillary carcinoma.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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